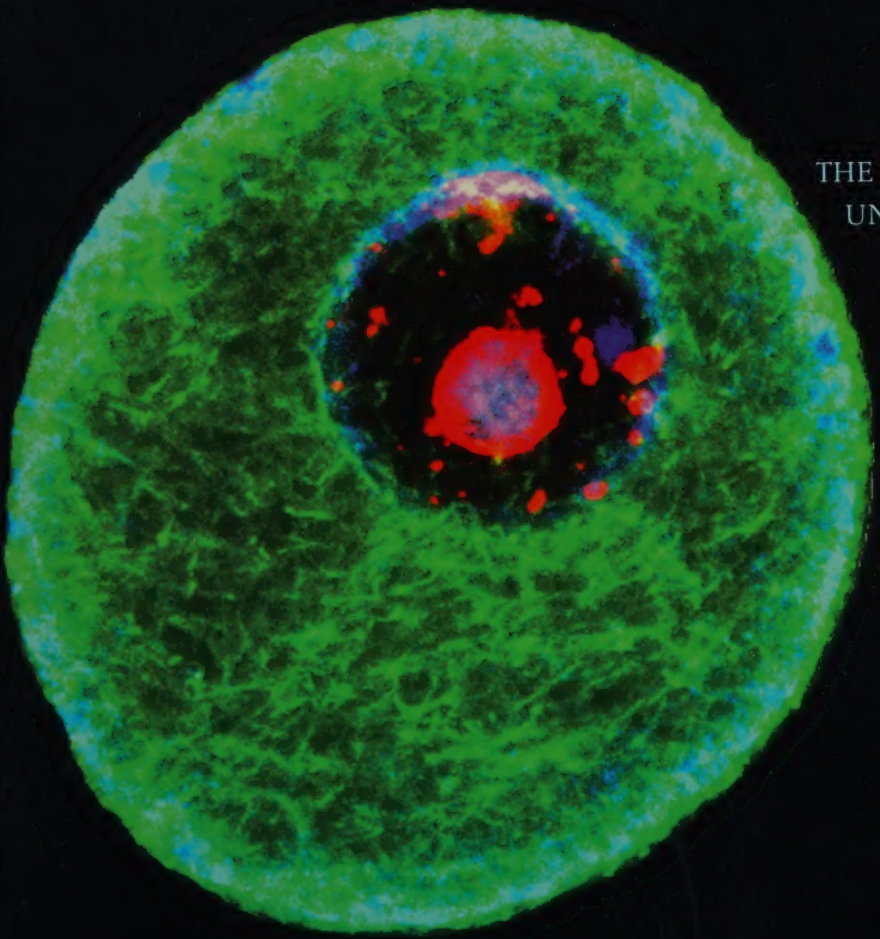
THE WELLCOME TRUST
Institute of Cancer and Developmental Biology
CANCER RESEARCH CAMPAIGN



1999

THE WELLCOME/CRC INSTITUTE
UNIVERSITY OF CAMBRIDGE

PROSPECTUS
1999

ANNUAL REPORT 1998

University of Cambridge

oskar mRNA localisation in a *Drosophila* oocyte
expressing *Musca domestica* Staufen protein
(David Micklem and Daniel St Johnston)

CONTENTS

FOREWORD BY THE CHAIRMAN 5
RESEARCH TOPICS 8
SCIENTIFIC STAFF OF THE INSTITUTE 41
CATEGORIES OF APPOINTMENT
POSTGRADUATE OPPORTUNITIES
MEMBERS OF THE INSTITUTE 42
SUPPORT STAFF 47
PUBLICATIONS 48
OTHER ACTIVITIES ETC. 55

Front cover: Expression of polo-like kinase in the mouse oocyte (Florence Wianny)
Rear cover: Relaxing at the Retreat 1998

WITHIN THE INSTITUTE

During the past year, the Institute has remained at the full level of occupancy that existed last year. We have about 50 graduate students from various countries together with somewhat more postdoctoral workers. We have 16 independent research groups. Each group obtains its major funding from one of our principal sponsors: the Wellcome Trust or the Cancer Research Campaign. Each group is affiliated to one of the Departments of Cambridge University, and we now have connections of this kind with the Departments of Anatomy, Biochemistry, Genetics, Medical Genetics, Pathology, Physiology and Zoology.

During this year, Michael Akam took up his position as Professor of Zoology and Director of the University Museum of Zoology, where he has moved with his group to pursue his interest in the evolutionary aspects of development. His place has been taken in the Institute by Dr Julie Ahringer who was elected to a Senior Research Fellowship of the Wellcome Trust and moved to our Institute with her group during the summer of 1998. She is analysing the earliest events of nematode development, with a special interest in the mechanisms that orient cell division axes. The result of these oriented cell divisions is that localized components of the egg and embryo are segregated to different daughter cells, thereby directing growth and subsequent differentiation of the early embryonic cells.

Several senior postdoctoral research workers won competitive awards for independent support this year. Whilst still associated with the groups in which they have worked, the awards enable these young scientists to embark on independent directions of research. The recipients of these awards are listed on page 46.

Congratulations are due to Ron Laskey, who was presented with the Louis Jeantet Prize for Medicine during 1998 (right). The recipients of other honours and awards are listed on page 55.

HISTORICAL BACKGROUND

The institute is situated in the middle of the area containing the science departments of the University of Cambridge and within a short distance from the centre of the historic city. It was founded in 1989 to promote research in the areas of developmental biology and cancer biology and is an assemblage of independent research groups located in one building designed to promote as much interaction as possible. Developmental and cancer biology are complementary since developmental biology is concerned with how cells acquire and maintain their normal function, whereas cancer is a result of a cell breaking loose from its correct controls and becoming abnormal. Both areas require a detailed knowledge of intercellular processes, which need to be analysed at the cellular and molecular levels.

These research areas are complementary at the scientific and technical levels. To understand what goes wrong when a cell becomes cancerous requires a knowledge of the processes that ensure correct function in normal development. At the technical level, the analysis of cellular and molecular processes requires familiarity with techniques that no one person can master, such as gene cloning, antibody preparation, cell culture, and embryonic manipulation. There is, therefore, a major benefit in having scientists with different but complementary knowledge and technical skills working in close proximity to one another.

John Gurdon.

John Gurdon, Chairman.

ORGANISATION AND FACILITIES

The Institute continues to grow. Since we started nine years ago, there has been a steady increase in the number of people working here (now about 200), the number of papers published each year, and our grant income. The 16 autonomous groups each secure funds in open national competition, as a result of appraisal entirely outside this Institute. We also enjoy the full support of Cambridge University, which funds most of our Senior Group Leader posts.

In accord with our increasing level of activity, we are fortunate in having increasingly sophisticated equipment and instrumentation. Apart from the usual equipment required for molecular biology and biochemistry, we have three confocal microscopes. All major equipment is available to all groups, and therefore is used very efficiently.

Our involvement in the University of Cambridge activities continues. All of our group leaders, many postdoctoral fellows and graduate students contribute to the undergraduate and graduate teaching of the University. As an Institute, we run a successful series of graduate seminars in developmental biology, contributed to and attended by members of most of the University biology departments.

We greatly welcome the occupation of the new Biochemistry building adjacent to us, which now houses most members of that department. The Biochemistry Department in Cambridge has great expertise and an outstanding reputation in the field of structural biology, and this complements the cell and developmental work of our Institute. We look forward to increasing levels of collaboration with the new Biochemistry Department.

Winners of the Mixed Team category, annual Cambridge Chariots of Fire Race

We are studying how patterns of cell divisions and cell fates are controlled during embryogenesis, using the nematode *C. elegans* as a model system. *C. elegans* is an excellent animal for studies in developmental biology because it grows rapidly (3 days from egg to adult), it is transparent (allowing all cells to be seen and followed in live animals), genetic analyses are fast and easy, molecular studies are rapid (the genome is completely sequenced), and it is beautiful. We have focused on two embryonic patterning events: the choice of the axis of cell division early in development and the patterning of posterior tissues later in embryogenesis.

One of the first indications of pattern in the *C. elegans* embryo is the orientation of the axis along which a cell divides. Although this is a widespread phenomenon in the development of many animals, little is known about how correct axes are chosen. We have shown that the β subunit of a heterotrimeric G protein is required for the correct orientation of early embryonic cleavage axes. We are currently screening for other genes involved to understand better how axis choice is made and what polarity cues are used.

Subsequent patterning events establish the body plan and the organisation of tissues. We are studying how the posterior end is patterned. This work is centred on the gene *vab-7,* which encodes an *even-skipped* homologue required for patterning posterior mesodermal and epidermal tissues in the embryo. We are using genetic and molecular methods to identify and study new genes involved in embryonic patterning to extend the pathway from *vab-7,* and to study the nature of the gene interactions. For example, we recently found that the gene *egl-27* genetically interacts with *vab-7* and encodes a component of a chromatin regulatory complex. As *vab-7* has a sequence and expression pattern similar to those of *even-skipped* homologues in other animals, including vertebrates, this work should be directly relevant to other systems.

Ahringer, J. (1997). Turn to the Worm! **Curr. Opin. Genet. Dev,** *7,* 410–415.

Ahringer, J. (1997). Maternal control of a zygotic patterning gene in *C. elegans.* **Development,** *124,* 3865–3869.

Zwaal, R., Ahringer, J., Rushforth, A., Anderson, P., and Plasterk, R. (1996). G proteins are required for spatial orientation of early cell cleavages in *C. elegans* embryos. **Cell,** *86,* 619–629.

Ahringer, J. (1996). Posterior patterning by the *Caenorhabditis elegans even-skipped* homolog *vab-7.* **Genes Dev.,** *10,* 1120–1130.

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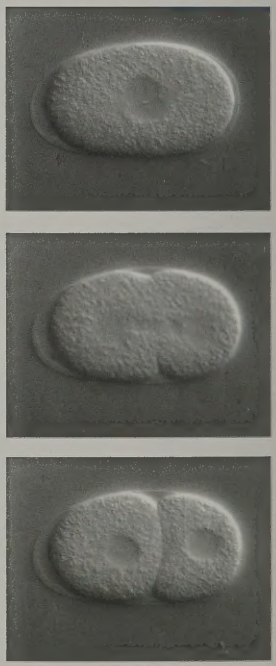
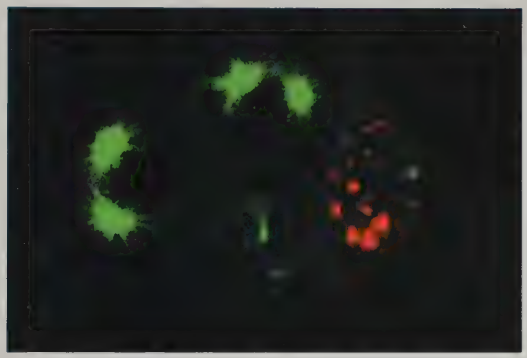
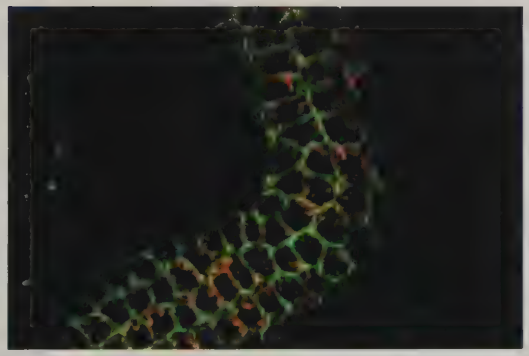


Cell divisions are easily followed in live embryos

vab-7 mutant larva (bottom) has severe posterior defects





Top: A four-cell embryo showing localisation of P-granules to the posterior (red) and microtubules emanating from the asters (green).
Bottom: Localisation of GPB-1 (green), a heterotrimeric G protein subunit, to the membrane in the germ line. P-granules (red).

The vertebrate embryo is organised and patterned by a series of inductive events. As our long term goal, we would like to understand the molecular basis of these inductions.

To facilitate our studies, we recently developed a method to generate transgenic frog embryos. We are using this technique to study the role of signalling by fibroblast growth factor (FGF) during mesoderm induction in the frog *Xenopus laevis*. To address the role of FGF receptor signalling during gastrulation, we have generated transgenic embryos that express a dominant-negative FGF receptor specifically during the gastrula stages. The resulting embryos fail to gastrulate and have severely disrupted mesoderm. We are now isolating downstream targets of the FGF receptor-signalling pathway to understand better how mesoderm formation occurs.

We are also studying how mesoderm pattern is established during the gastrula stages. We have begun to investigate the regulation of two early mesodermal genes expressed in transgenic embryos. One of these genes, *Xnot*, is expressed in dorsal mesoderm that is destined to become notochord. The other gene, *XMyf-5*, is a myogenic gene expressed in dorso-lateral mesoderm destined to become muscle.

Another focus of our interest is the role of growth factor signalling in heart and eye development. We are generating transgenic embryos that aberrantly express in these organs genes that upregulate or downregulate growth factor signalling molecules.

Finally, we are performing insertional mutagenesis using gene trap approaches in *Xenopus tropicalis*, a diploid frog related to *Xenopus laevis*, with a view to screening for novel developmental genes in *Xenopus tropicalis*.

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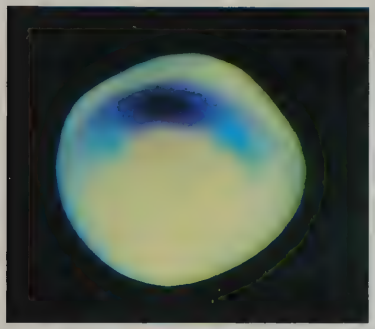
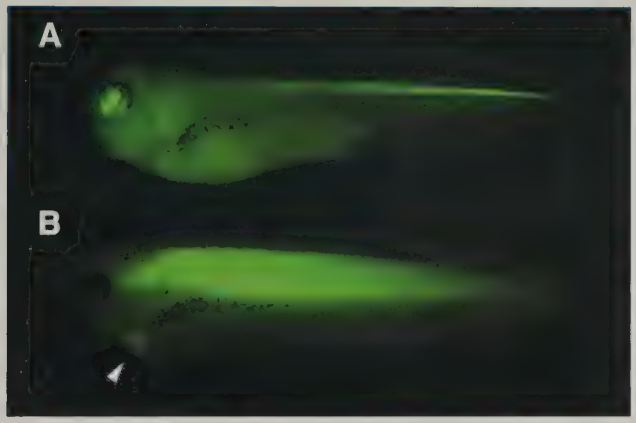
Kroll, K.L., and Amaya, E. (1996). Transgenic *Xenopus* embryos from sperm nuclear transplantations reveal FGF signalling requirements during gastrulation. **Development** *122*, 3173–3183.

Amaya, E., Offield, M.F., and Grainger, R.M. (1998). Frog genetics: *Xenopus tropicalis* jumps into the future. **Trends Genet.** *14*, 253–255.

Kroll, K.L., and Amaya, E. (1998). Transgenic frogs: A revised method for producing transgenic *Xenopus* embryos by nuclear transplantation. *In* Early Development of *Xenopus laevis*, H.L. Sive, R.M. Grainger, and R.M. Harland, eds. (NY: Cold Spring Harbor Laboratory Press), in press.



An early gastrula stage embryo stained for the expression of *Xnot* (dark purple) and *Xmyf-5* (light blue).



Transgenic embryos expressing green fluorescent protein (GFP) using promoter fragments isolated from the *Xotx-2* (panel A) and muscle actin (panel B) genes. Arrowhead in panel B shows GFP expression in the developing heart.

An adult *Xenopus laevis* female (left) and an adult *Xenopus tropicalis* female (right).

As the nervous system develops, thousands of neurons are born, each of which must assume a specific identity. One way to generate cell diversity is to ensure that, upon cell division, each daughter cell adopts a different fate. This can be most simply achieved by asymmetric segregation of cell fate determinants at cell division. Recently, it has been shown that such a mechanism is used to direct cell fates during *Drosophila* neurogenesis. Each neuronal precursor cell (or neuroblast, NB) undergoes a series of stem cell divisions. Prior to each division, the homeodomain protein Prospero is localised to the basal side of the cell, and is then partitioned to the daughter cell (or ganglion mother cell, GMC). The mRNA encoding Prospero is segregated similarly.

We are investigating the molecular mechanisms that direct the asymmetric segregation of cell fate determinants. We have shown that Staufen, a double-stranded RNA-binding protein, binds to the *prospero* mRNA and directs its subcellular localisation. Both Staufen and Prospero, in turn, bind to Miranda, which mediates their basal localisation at mitosis. To follow the asymmetric localisation of determinants in living embryos, we fused green fluorescent protein (GFP) to Staufen, Prospero and Miranda. We are using colour variants of GFP to label several different proteins at once *in vivo*.

Using targeted gene expression, transcription patterns in neuronal precursor cells and in their progeny can be altered with the aim of eliciting specific cell fate changes. In this way, we are investigating the role of segmentation genes in directing neuronal and glial cell fates. We can also express toxins in a restricted fashion to ablate cells and eliminate cell–cell interactions. We are studying the neuron–glial interactions that direct axon outgrowth and mediate cell survival. Neurons and glia are labelled in living embryos with tau-GFP, which highlights microtubules. We can then trace individual cells throughout embryogenesis.

Schuldt, A.J., Adams, J.H.J., Davidson, C.M., Micklem, D.R., Haseloff, J., St. Johnston, D., and Brand, A.H. (1998). Miranda mediates asymmetric protein and RNA localisation in the developing nervous system. **Genes Dev.**, *12*, 1847–1857.

Dormand, E.L., and Brand, A.H. (1998). Runt determines cell fates in the *Drosophila* embryonic CNS. **Development**, *125*, 1659–1667.

Schuldt, A.J., and Brand, A.H. (1999). Mastermind acts downstream of Notch to specify neuronal cell fates in the *Drosophila* CNS. **Dev. Biol.**, *205*, 287–295. *For further publications see page 48.*

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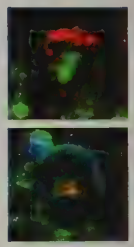
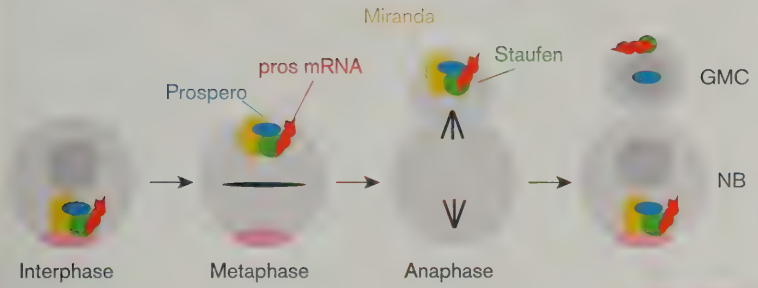


prospero mRNA (red, top panel), Prospero protein (blue, bottom panel) and Staufen protein (green, bottom panel), form basal crescents in neuroblasts.

In a time course of a living embryo, Staufen-GFP forms a crescent on the basal side of the neuroblast before being partitioned to the daughter cell.



Miranda coordinates the asymmetric segregation of Prospero protein and its mRNA in neural precursor cells (NB). Miranda binds directly to both Prospero and Staufen which, in turn, binds *prospero* mRNA. The complex moves from the apical (bottom) to the basal (top) side of the cell, and is segregated to the daughter cell (GMC) at cytokinesis.

(Left) Axon outgrowth in living embryos. Pioneer neurons expressing tau-GFP were imaged by two-photon microscopy.

(Right) Cells labelled with DiI (red) transplanted next to the ventral midline (blue) of the embryonic CNS. Axons are labelled in green.

More information can be found on the Brand Lab home page:
http://www.welc.cam.ac.uk/~brandlab/

Cellular adhesion and communication are vital during the development of multicellular organisms. These processes are initiated by proteins on the surface of cells that can stick cells together or transmit signals across the plasma membrane. Members of one family of cell surface receptors called integrins can perform both of these functions, and thus provide a molecular link between cell adhesion and signalling. Our research is focused on determining how integrins work with proteins inside the cell, including cytoskeletal and signalling molecules, to hold cell layers together and ensure their appropriate differentiation during development.

To discover what other proteins are required to work with integrins, we have used the genetic tools available to study the fruit fly *Drosophila,* and we have isolated 10 new genes that are required for integrin-mediated adhesion. The first of these genes we have characterised at the molecular level encodes a large cytoskeletal linker protein that is similar to plectin and dystrophin. Plectin links integrins to the cytoskeleton in vertebrate epidermal cells, and mutations in the human gene cause a severe loss of adhesion of the skin, emphasising the conservation of integrin adhesion mechanisms in humans and flies. Analysis of the other genes we identified is currently under way.

We have recently identified genes in *Drosophila* that require integrin function for their normal pattern of expression, and demonstrated that these genes are regulated by a signal transduction pathway starting at integrin intracellular domains. These experiments provide us with tools that are essential for a genetic dissection of integrin signalling.

Walsh, E.P., and Brown, N.H. (1998). A screen to identify *Drosophila* genes required for integrin mediated adhesion. **Genetics** *150,* 791–805.

Gregory, S.L., and Brown, N.H. (1998). *kakapo,* a gene required for adhesion between and within cell layers in *Drosophila,* encodes a large cytoskeletal linker protein related to plectin and dystrophin. **J. Cell Biol.** *143,* 1271–1282.

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For further publications see page 48.

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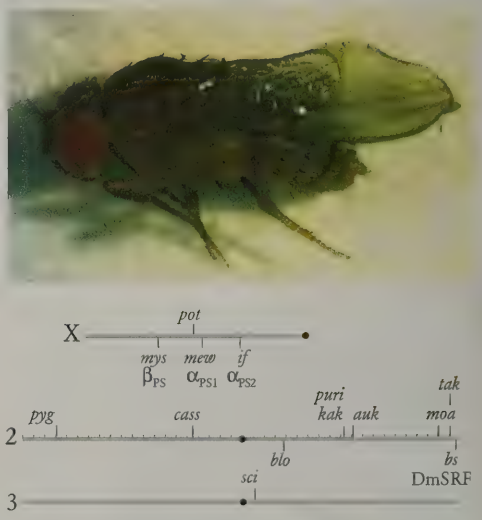
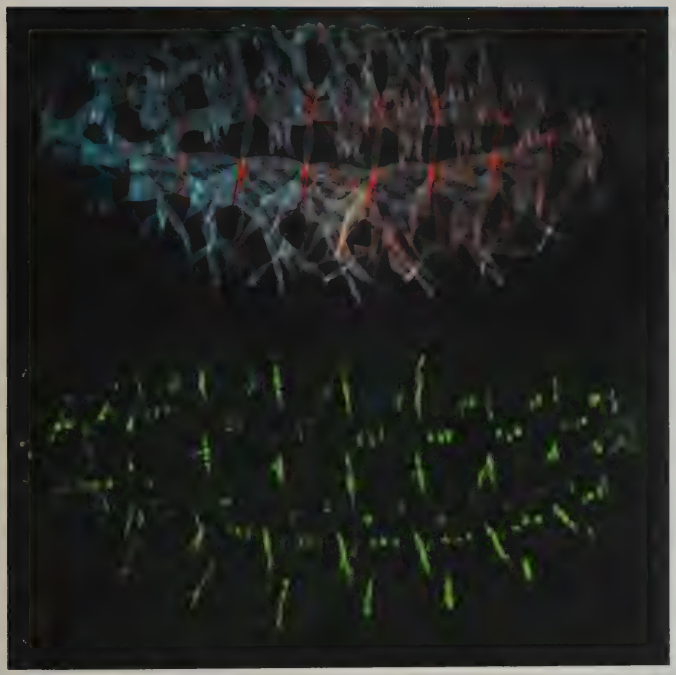


Tóp: Loss of adhesion between the wing surfaces is caused by mutations in integrin genes.
Bottom: Loci in the *Drosophila* genome that cause loss of adhesion in the wing.



The cystoskeletal linker protein *Kakapo* (bottom panel, green) is expressed in the epidermal cells that require integrins (top panel, red) to attach to the muscles (top panel, blue).

Expression of an integrin target gene in the larval midgut.

Our overall strategy and interest is in an Experimental Mammalian Genetics which is made possible through the use of embryonic stem (ES) cells of mice as a route to somatic and germ-line transgenesis. Because these cells provide a bridge between the whole animal and tissue culture, specific genetic modification, which may be induced, screened or selected in culture, can be tested and recombined within the context of the physiology and genetics of the whole animal.

We are creating mutants both by targeting and gene trapping to introduce specific mutations through ES cells in mice.

One example of a gene putatively involved in early development is the T-box gene, Eomesodermin. A disrupted allele at this locus introduces the *lac-z* reporter gene under the control of the endogenous promoter (EoLacZ). Some heterozygotes show gastrulation defects and holoprosencephaly. Homozygote embryos fail at an early stage. Both extraembryonic and embryonic tissues are affected. Aggregation experiments with homozygous (-/-) ES cells demonstrate a block in the epiblast at gastrulation.

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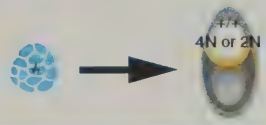
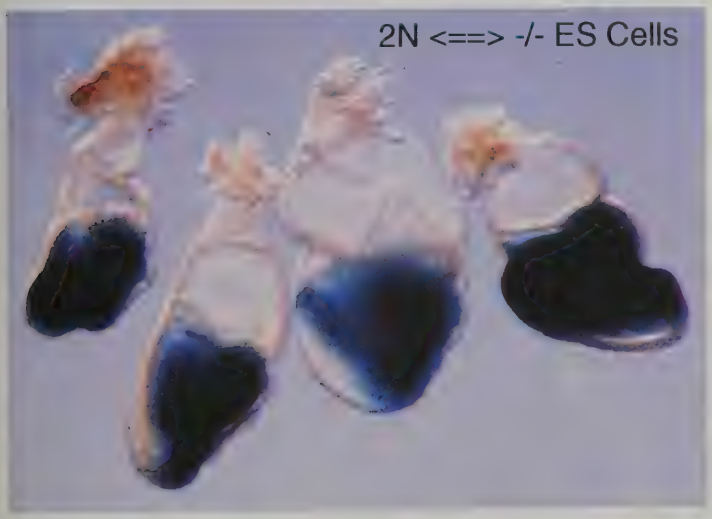
Gilmour, D.T., Lyon, G.J., Carlton, M.B.L., Sanes, J.R., Cunningham, J.M., Anderson, J.R., Hogan, B.L.M., Evans, M.J., and Colledge, W.H. (1998). Mice deficient for the secreted glycoprotgein SPARC/OSTEONECTIN/BM40 develop normally but show severe age-onset cataract formation and disruption of the lens. **EMBO J.** *17(7),* 1860–1870.

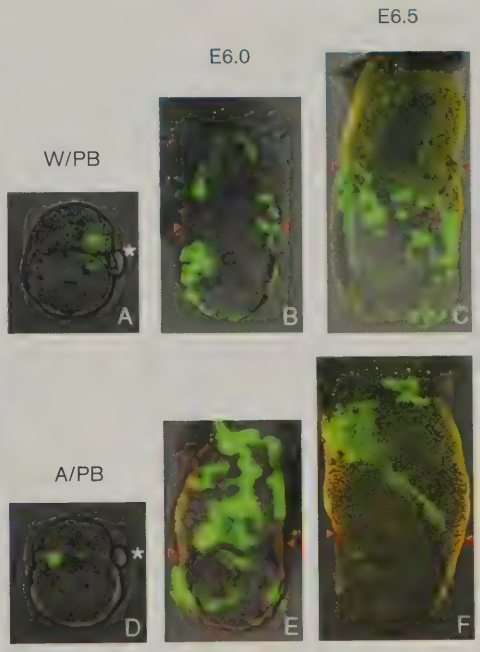
Wattler, S., Russ, A., Evans, M.J., Nehls, M. (1998). A combined analysis of genomic and primary protein structure defines the phylogenetic relationship of new members of the T-box family. **Genomics,** *48 (1),* 24–33.

For further publications see page 49.

Chimeras were generated by combining wild type host embryos with ES cells homozygous for EoLacZ. The mutant cells are stained for LacZ expression (blue).







Above: An example of lineage tracing. Micro injection of GFP mRNA into an inner cell mass either adjacent to or opposite to the residual polar body demonstrates in the resulting postimplanation embryos a differential fate indicating that there is a polarity already established by the blastocyst stage.

EoLacZ heterozygotes show holoprosencephaly with low penetrance

To understand cell behaviour in the developing mammalian central nervous system (CNS), we have focused on the role of two families of cell adhesion molecules; integrins and cadherins.

By studying two different types of neural cells grown in culture – neural precursor cells of the germinal zones grown as neurospheres and committed progenitor cells of the oligodendrocyte lineage – we found that different integrins are expressed at distinct stages of differentiation. Each of these integrins regulates different aspects of cell proliferation, migration, differentiation and survival. This suggests that switching of integrin expression is an important cue for changing cell behaviour in the developing CNS. Our current work tests this hypothesis using targeted gene disruption in mice and expression of chimeric integrin subunits, as well as experiments to determine the signalling pathways downstream of integrins and their interactions with those pathways regulated by growth factors and other extracellular signalling molecules.

Our work on cadherins has focused on the protocadherin encoded by the *fat* gene, a homologue of a *Drosophila* tumour suppressor gene. We showed that this gene is expressed in the germinal neuroepithelium throughout life and, by using a combination of transgenic and cell-culture experiments, we are currently testing the hypothesis that this molecule regulates cell proliferation and migration in the neuroepithelium.

An important goal of this work is to apply our understanding of developmental neurobiology to the question of brain repair. We have shown that successful repair in peripheral nerve is associated with re-expression of embryonic forms of the extracellular matrix molecules that are recognised by specific integrins. Re-expression of these integrins in adult tissues may therefore facilitate repair following injuries that do not normally repair, such as those seen in multiple sclerosis or stroke.

Jacques, T.S., Nishimura, S., Pytela, R., Edwards, G.M., Streuli, C.H., and ffrench-Constant, C. (1998). Neuroepithelial cell chain migration and division are regulated through different β1 integrins. **Development** *125*, 3167–3177.

Ponassi, M., Jacques, T., Ciani, L., and ffrench-Constant, C. (1999). Expression of the rat homologue of the *Drosophila fat* tumour suppressor gene. **Mech. Dev.**, in press.

For further publications see page 50.

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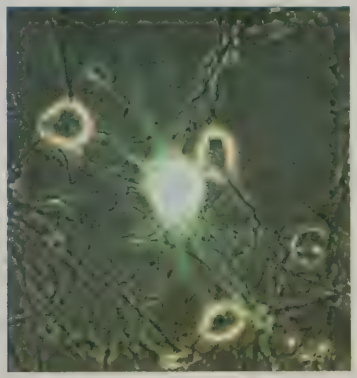
GFP-expressing oligodendrocyte precursor in co-culture with axons



Oligodendrocyte in cell culture

Signalling between cells is the single most important mechanism that brings about cell differentiation in vertebrate development. In general, cells in one region of an embryo synthesize and secrete proteins that determine the path of differentiation of cells nearby. In several cases, cells are now known to activate different genes according to the concentration of a single signalling molecule, which is therefore described as a morphogen.

We have developed methods to expose naïve blastula cells of *Xenopus* to defined concentrations of activin, a transforming growth factor (TGF) β-family molecule. Activin is a candidate for the natural inducer of mesodermal differentiation which takes place a few hours after fertilization. Cells respond to activin by transcribing various mesodermal genes in a concentration-dependent way. We find that they do this by measuring the absolute number of activin-occupied receptors of one type.

Our overall aim is to understand the mechanism of concentration-dependent signalling between cells in development. In addition to analysing how cells measure the concentration of an external signalling factor, we determine how signals are transduced quantitatively through the cytoplasm to the nucleus. As part of this programme, we analyse the mechanism of activation of two key mesodermal genes, *Eomesodermin* and *Antipodean;* both were discovered in this laboratory two years ago, and both encode T-domain transcription factors.

To understand how embryonic cells are made to differentiate may help, eventually, to reveal ways of redirecting cancer cells from uncontrolled proliferation to a differentiated state.

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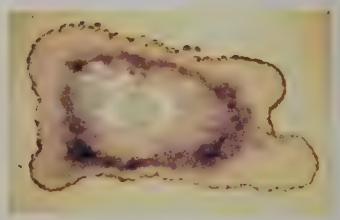

Activin-loaded beads send out a ripple of *Xbra* expression through a static field of responsive blastula cells. *Eomes* is expressed in the cells between the beads and the *Xbra* ripple.

Crease, J. D., Dyson, S., and Gurdon, J. B. (1998). Cooperation between the activin and Wnt pathways in the spatial control of organizer gene expression. **Proc. Natl. Acad. Sci. USA** *95,* 4398–4403.

Dyson, S., and Gurdon, J. B. (1988). The interpretation of position in a morphogen gradient as revealed by occupancy of activin receptors. **Cell** *93,* 557–568.

Gurdon, J. B., Dyson, S., and St Johnston, D. (1998). Cells' perception of position in a concentration gradient. **Cell** *95,* 159–162.

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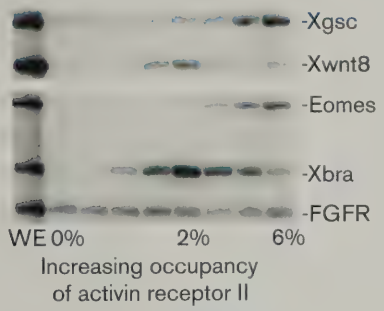
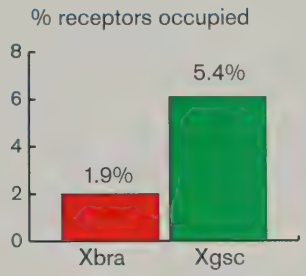
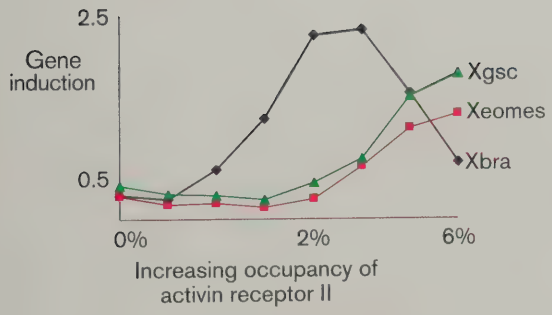
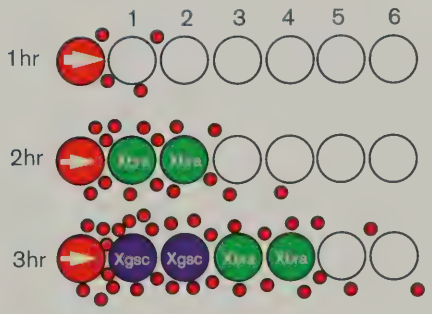




Cells switch gene response at remarkably low receptor occupancy



Gene activation is concentration dependent



Morphogen gradient formation

Our research aims to understand the molecular basis of DNA repair, DNA damage signalling and transcription. To this end, we are employing diverse approaches in bacterial, yeast and mammalian systems.

Our main focus in recent years is to determine how eukaryotic cells detect, respond to and repair DNA damage. For example, we are investigating how the human DNA-dependent protein kinase (DNA-PK) and its associated proteins function in the repair of ionizing radiation-induced DNA damage and in the process of V(D)J recombination – a mechanistically related process that helps generate the antigen-binding diversity of the vertebrate immune system.

As a result of studying DNA repair in yeast, we have established that yeast Ku, the homologue of the DNA-binding subunit of DNA-PK, also functions in telomere length maintenance, transcriptional silencing and retrotransposition. Our current goals in this area are to understand the mechanistic basis of these activities and to learn whether human Ku functions similarly.

We are also analysing relatives of the DNA-PK catalytic subunit (DNA-PKcs), ATM and ATR. ATM is defective in the human neurodegenerative and cancer predisposition syndrome, ataxia–telangiectasia. We found recently that, like DNA-PKcs, ATM can detect DNA double-strand breaks, and that ATM and ATR phosphorylate a key regulatory domain of the tumour suppressor protein p53. Through such work, we aim to understand better how cells repair double-strand breaks in their DNA and why defects in this process lead to cancer.

Our interest in transcription is focused on a branch of bacteria called Archaea. Our work has helped establish that transcription in these organisms is strikingly similar to that in eukaryotic cells, and we are using this feature of Archaea to define the mechanisms and evolution of transcriptional control.

Qureshi, S.A., and Jackson, S.P. (1998). Sequence-specific DNA binding by the *Sulfolobus shibatae* TFIIB homologue, TFB, and its effects on promoter strength. **Mol. Cell** *1*, 389–400.

Freire, R., Murguia, J.R., Tarsounas, M., Lowndes, N., Moens, P.B., and Jackson, S.P. (1998). Human and mouse homologues of *Schizosaccharomyces pombe rad1*$^{+}$ and *Saccharomyces cerevisiae RAD17*: linkage to checkpoint control and mammalian meiosis. **Genes Dev.** *12*, 2560–2573.

Boulton, S.J., and Jackson, S.P. (1998). Components of the Ku-dependent non-homologous end-joining pathway are involved in telomeric length maintenance and telomeric silencing. **EMBO J.** *17*, 1819–1828.

For further publications see page 50

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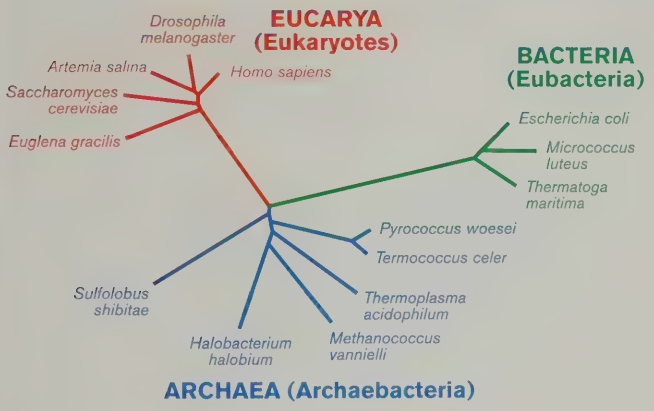
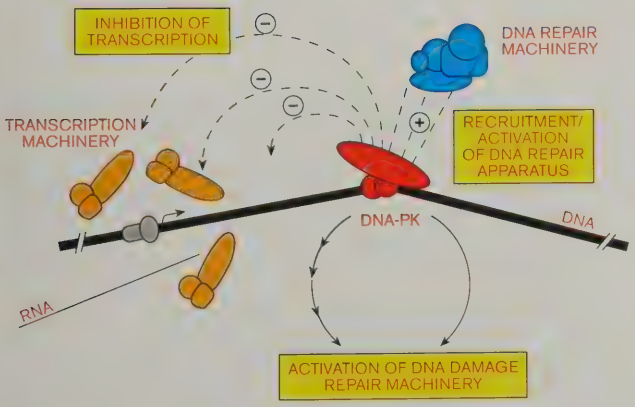
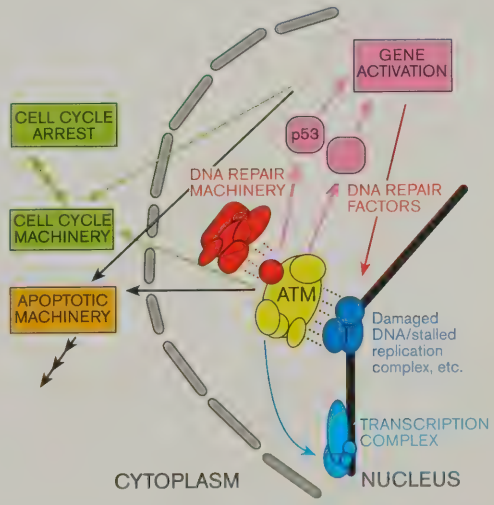


Archaea: the third domain of life. Despite lacking nuclei and being similar to eubacteria in morphology, Archaea are at least as remotely related to Bacteria as to Eucarya. By cloning archaeal transcription factors and establishing a reconstituted transcription system *in vitro*, we have discovered striking similarities between transcription in Archaea and in eukaryotic cell nuclei.



DNA-PK: a paradigm for DNA damage-sensing systems.
In the model, DNA-PK binds to damaged DNA and potentiates DNA repair and V(D)J recombination through the various mechanisms indicated.



Model for DNA-damage signalling by ATM. In association with other proteins, ATM recognizes DNA damage, then promotes DNA repair and signals the presence of DNA damage to p53 and to the cell cycle and apoptotic machineries.

TONY KOUZARIDES

Several transcription factors are implicated in the generation of cancer. Our group is interested in defining the mechanisms by which these factors modulate gene expression and regulate the proliferative state of the cell. The three main areas of research that we are involved in are outlined below.

The *CBP* gene is translocated in a subset of acute myeloid leukaemias. The CBP protein is called a co-activator because it can bind to and stimulate the activity of numerous DNA-binding transcription factors. We have found that CBP is an enzyme that acetylates histones, a modification that is thought to remodel chromatin. The histone acetyltransferase activity of CBP contributes to its transcriptional activation activity and may explain how CBP can augment the activity of numerous transcription factors.

The *Retinoblastoma (Rb)* tumour suppressor gene is mutated in numerous different cancers. Rb protein can induce cell cycle arrest by repressing S-phase genes regulated by the E2F transcription factor. We have found that Rb recruits a histone deacetylase activity to E2F and that this activity is required for Rb-mediated transcriptional repression. Mutations in Rb that occur in tumours prevent its association with histone deacetylase activity suggesting that this interaction is important for the tumour suppressor functions of Rb.

The *BRCA2* gene is mutated in a substantial proportion of familial breast cancer cases. Our analysis of BRCA2 protein suggests that one of its functions is to regulate transcription; it associates with the transcriptional regulator P/CAF and it has a transcriptional activation domain that is deleted in tumours.

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Brehm, A., Miska, E.A., McCance, D.J., Reid, J.L., Bannister, A.J., and Kouzarides, T. (1998). Retinoblastoma protein recruits histone deacetylase to repress transcription. **Nature** *391*, 597–601.

Martinez-Balbás, M., Bannister, A.J., Martin, K., Haus-Seuffert, P., Meisterernst, M., and Kouzarides, T. (1998). The acetyltransferase activity of CBP stimulates transcription. **EMBO J.** *17*, 2886–2893.

Milner, J., Ponder, B., Hughes-Davies, L., Seltmann, M., and Kouzarides, T. (1997). Transcriptional activation functions in BRCA2. **Nature** *386*, 772–773.

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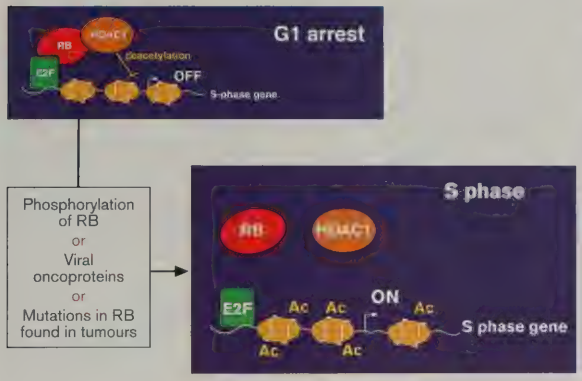
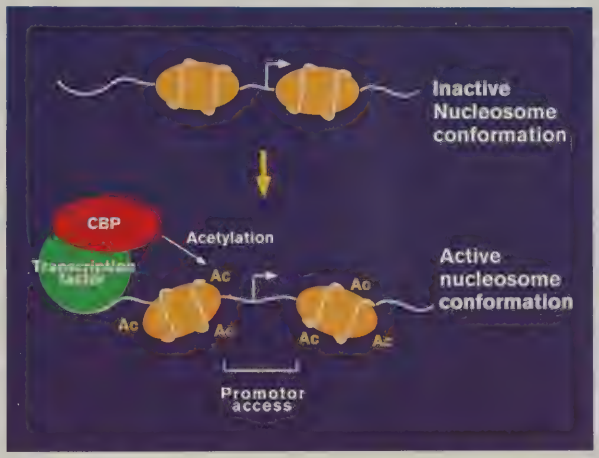
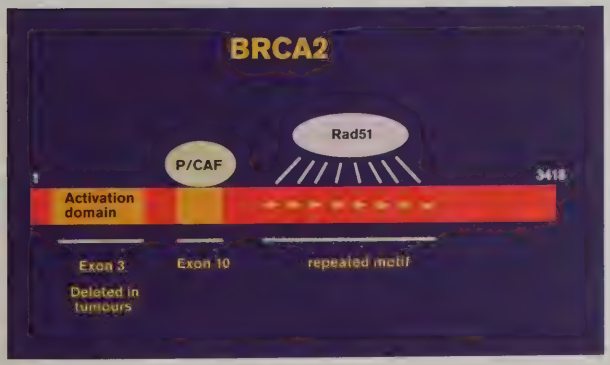


Rb represses E2F-regulated genes by recruiting histone deacetylase.



The CBP co-activator stimulates transcription by acetylating nucleosomal histones and remodelling chromatin.



The BRCA2 protein has characteristics of a transcription factor and a DNA repair protein.

Our current research focuses on two topics, the control of eukaryotic chromosome replication and DNA replication proteins as diagnostic cancer markers.

We have used human cells grown in culture to develop a family of cell-free systems that initiate DNA replication efficiently *in vitro*. We use G1 nuclei as templates and S-phase extracts to induce replication. We have focused our attention on proteins that regulate DNA replication by assembling a pre-replication complex on unreplicated DNA. These proteins are the origin recognition complex ORC, Cdc6 and proteins of the MCM family. The presence of MCM proteins distinguishes replicated DNA from unreplicated DNA as MCMs are displaced during replication.

Using the human DNA replication cell-free system, we have shown that competence of G1 nuclei to respond to S-phase factors arises suddenly in G1 at a time that coincides with synthesis of Cdc6 protein. Furthermore, addition of recombinant Cdc6 protein advances the time of initiation of DNA replication. This effect of exogenous Cdc6 protein depends on the state of the nuclear envelope of the template nuclei, a phenomenon that we are continuing to study.

Cdc6 and MCM proteins can be used as markers for proliferating cells at any stage in the cell division cycle except quiescence (G0). We have exploited this to develop an immuno-enhanced cervical smear test in order to decrease the frequency of false-negative results in this important test. We are able to combine immunostaining for MCM5 or Cdc6 together with the conventional Papanicolaou stain. In this way, both types of information can be read from the same slide. We are attempting to extend this approach to other forms of cancer.

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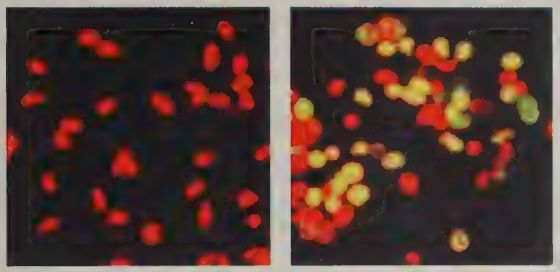
Krude, T., Jackman, M., Pines, J., and Laskey, R.A. (1997). Cyclin/Cdk-dependent initiation of DNA replication in a human cell-free system. **Cell** *88*, 109–119.

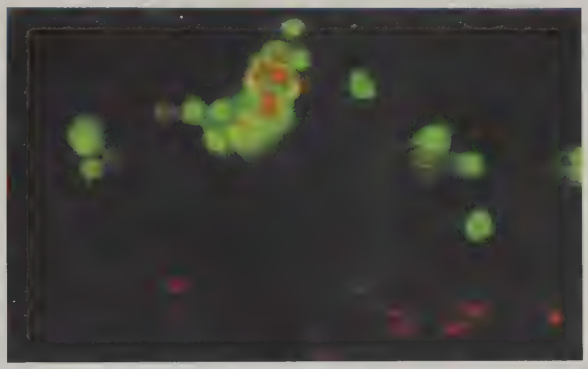
Stoeber, K., Mills, A.D., Kubota, Y., Krude, T., Romanowski, P., Marheineke, K., Laskey, R.A., and Williams, G.H. (1998). Cd6 protein causes premature entry into S phase in a mammalian cell-free system. **EMBO J.** *17*, 7219–7229.

Williams, G.H., Romanowski, P., Morris, L., Madine, M., Mills, A.D., Stoeber, K., Marr, J., Laskey, R.A., and Coleman, N.C. (1998). Improved cervical smear assessment using antibodies against proteins that regulate DNA replication. **Proc. Natl. Acad. Sci. USA** *95*, 14932–14937.

For further publications see page 52.

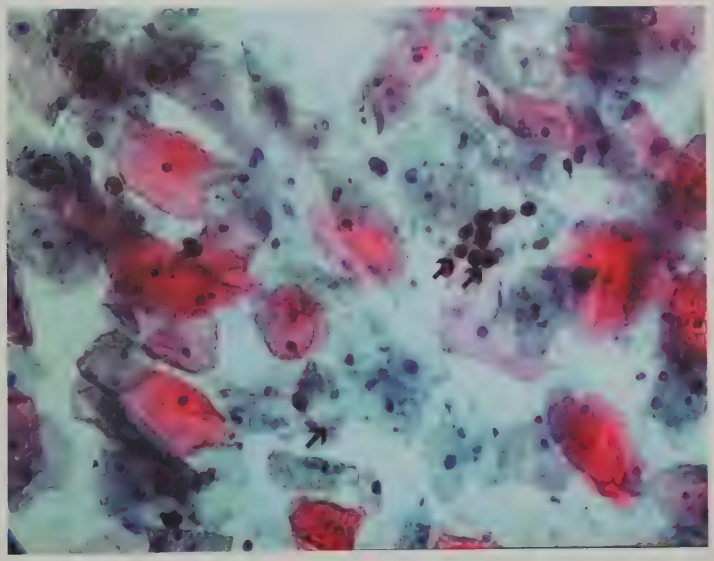


3T3 Cell nuclei in buffer (left) or in S-phase cytosol (right)



Enhanced cervical smear (Pap) test by fluorescence microscopy

Enhanced cervical smear (Pap) test



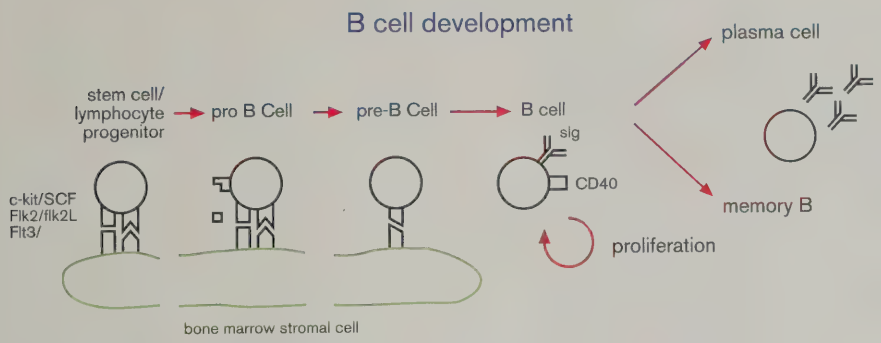
My laboratory is interested in the nuclear factors that govern B lymphocyte development. As a model system, we are concentrating on the immunoglobulin (Ig) κ3' enhancer, initially using transformed B cell lines to identify transcription factors that are important for the function of this element. Recently, however, we have examined the behaviour of κ3' enhancer in transgenic mice which has allowed us to examine the signalling pathways and nuclear mediators that lead to enhancer activation in primary B cells. We have identified at least three different pathways leading to increased transcriptional activity through this enhancer: treatment with phorbol myristic acid (PMA) and/or ionomycin, stimulation by lipopolysaccaride (LPS), and cross-linking of surface IgM. A unique NFAT transcription complex is responsible for PMA/ionomycin induction, whereas this factor is not required for signalling by LPS or IgM cross-linking. Treatment with LPS, by contrast, leads to the upregulation of the transcription factor E47, which is essential for enhancer function.

We have also examined the effect of CD40 signalling on enhancer activation and found that induction of B-cell proliferation through this receptor is not sufficient to cause enhancer activation. In fact, CD40 transmits a negative signal that prevents LPS- and anti-μ-mediated enhancer activation. At the molecular level, CD40 appears to act by preventing E47 induction. Interestingly, mRNA levels for E47 do not increase after LPS stimulation, and they remain unchanged after co-cross-linking of CD40. Thus E47 appears to be regulated at the protein level. We are investigating whether this is mediated by modulating the stability of the protein or by translational control. In addition, we have preliminary evidence that the Lyn protein tyrosine kinase is responsible for initiating the CD40-mediated repression.

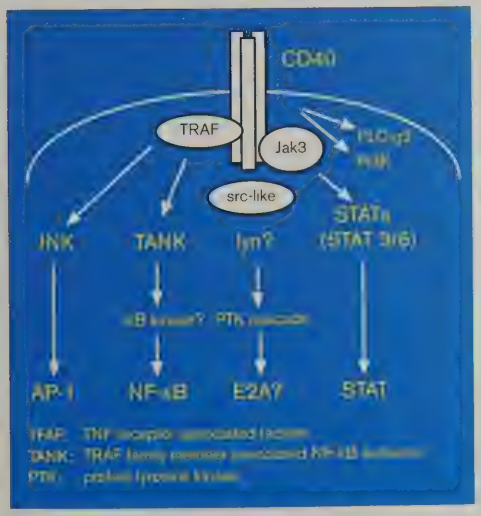
CO-WORKERS: DINA MUFTI

Meyer, K.B., and Ireland, J. (1998). PMA/ionomycin induces Igκ 3' enhancer activity which is in part mediated by a unique NFAT transcription complex. **Eur. J. Immunol.** *28,* 1467–1480.

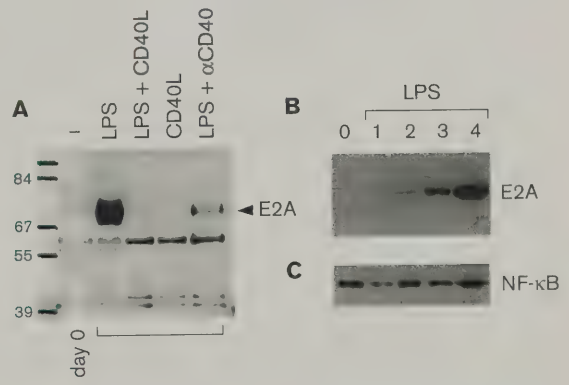
Meyer, K.B. (1999). Induction of the Igκ 3' enhancer by distinct pathways can be inhibited by crosslinking of the CD40 receptor. **Eur. J. Immunol.,** *29,* in press



Schematic representation of B cell development



Phosporylation cascades and nuclear targets activated by CD40 signalling



E2A is the target of LPS and CD40 signalling. (A) Presence of E2A protein in primary B cells before and after 3 days of culture with LPS, LPS plus CD40 ligand (L), CD40L alone or LPS plus anti-CD40 antibody. (B and C) Time-course analysis of E2A and NF-κB induction after LPS stimulation of primary B cells.

During embryonic development, precursor cells of the vertebrate central nervous system are induced in the dorsal ectoderm by signals from the organiser. Neuroectodermal cells exit the cell cycle and start differentiating in a stereotypical spatial and temporal pattern. The central interest in our lab is to understand the mechanisms by which neuronal differentiation in the vertebrate nervous system is temporally and spatially controlled. As a model system, we use the frog *Xenopus laevis* and a combination of molecular and classical embryology.

We are investigating the role of several transcription factors in controlling the pattern of neurogenesis in *Xenopus* ectoderm. We have isolated *XBF-1*, a winged helix transcription factor which shows restricted expression in the anterior neural plate, from which the telencephalon is derived. Functional analysis of *XBF-1* suggests that it is bifunctional, acting as a suppressor or an activator of neuronal differentiation at a high and low concentration, respectively. We have proposed that this dual activity is utilised *in vivo* to position neuronal differentiation around an area of high *XBF-1* expressing cells. The molecular mechanism by which *XBF-1* exerts a dual effect on neurogenesis is currently being investigated.

We are also interested in the molecular characterisation of neural precursor cells. We have shown that *Xiro3*, a homeobox transcription factor, is expressed early in the neural plate and functions to specify a neural precursor fate. We are analysing additional early neural genes such as a homeobox gene similar to the *Drosophila distal-less* gene, *X-dll3*, which is also expressed in the anterior neural plate.

Through functional analysis of these early neural genes and identification of their targets, we aim to understand how the processes of patterning and neurogenesis are integrated.

Bourguignon, C., Li, J., and Papalopulu, N. (1998). *XBF-1*, a winged helix transcription factor with dual activity, has a role in positioning neurogenesis in *Xenopus* competent ectoderm. **Development**, *125*, 4889–4900.

Bellefroid, E.J., Kobbe, A., Gruss, P., Pieler, T., Gurdon, J., and Papalopulu, N. (1998). *Xiro3* encodes a *Xenopus* homolog of the *Drosophila Iroquois* genes and functions in neural specification. **EMBO J.**, *17*, 191–203.

CO-WORKERS: PENNY DAY
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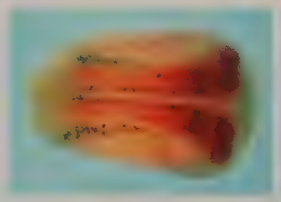
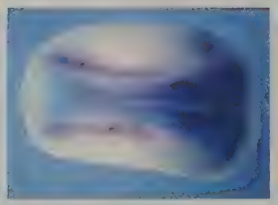
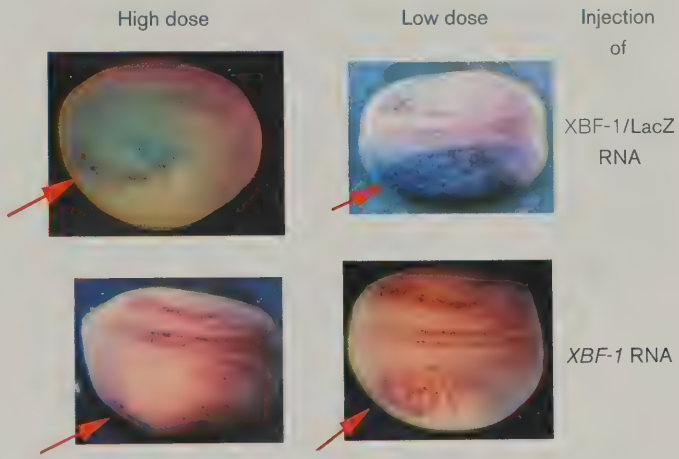


Xiro3/N-tub

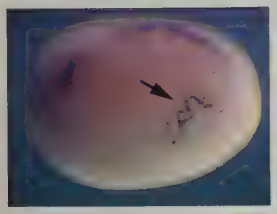


XSox3/N-tub

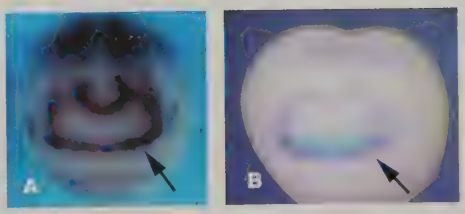
Xiro3 (red) and *XSox3* (light blue) are expressed in neural precursor cells that are located between the medial and intermediate stripes of neuronal differentiation (marked by N-tubulin; brown or magenta) in the posterior neural plate



Misexpression of a high concentration of *XBF-1* suppresses endogenous and induces ectopic N-tubulin at the boundary of the expressing ectoderm. Misexpression of a low concentration of *XBF-1* only induces additional N-tubulin within the expressing ectoderm. N-tubulin expression on the injected side is indicated by a red arrow



A clone of cells in the epidermis of a *Xenopus* embryo produced by injection of lacZ (light blue) and *XBF-1* in one cell of the 32-cell-stage embryo. Ectopic neuronal differentiation, marked by N-tubulin expression (brown, arrow), surrounds the clone of *XBF-1*/lacZ expressing cells (light blue)



In the anterior neural plate, neurogenesis occurs in two curved stripes, marked by the expression of *X-Delta-1* (brown in A, magenta in B). The anterior stripe (arrow in A and B) is located at the border of the *XBF-1* expression domain (light blue in B)

The dramatic changes in the architecture of the cell as it prepares to divide are orchestrated by the cyclin-dependent kinases (CDKs) and their cyclin partners. Our goal is to determine how cyclin–CDK activities are co-ordinated in space and time to reorganise the cell at mitosis and, in particular, how cyclins localise their CDKs to specific subcellular structures such as the mitotic spindle.

We are studying the dynamic behaviour of the mitotic cyclins during cell division in real time, in living cells, using chimaeras between cyclins and green fluorescent protein. We are visualising these proteins and their effect on cell architecture by time-lapse fluorescence and DIC video microscopy. We are defining the domains of the B-type cyclins that target them to the spindle and the Golgi, and the interactions between the cyclin–CDKs and other components of the cell cycle machinery. We are also using this assay to try to understand the mitotic role of cyclin A, and how cyclin proteolysis is co-ordinated with progress through mitosis.

We have found that the cyclin B1–cdc2 complex is constantly shuttling between the nucleus and the cytoplasm because its constitutive nuclear import is counteracted by continuous nuclear export. Moreover, in collaboration with Ron Laskey's group, we have found that mitotic cyclin–CDK complexes form a novel nuclear-targeting signal that is recognised and transported into the nucleus by the importin–β family, independent of importin α. We believe that the dynamic behaviour of cyclin B1–cdc2 is essential to its role in coordinating entry into mitosis.

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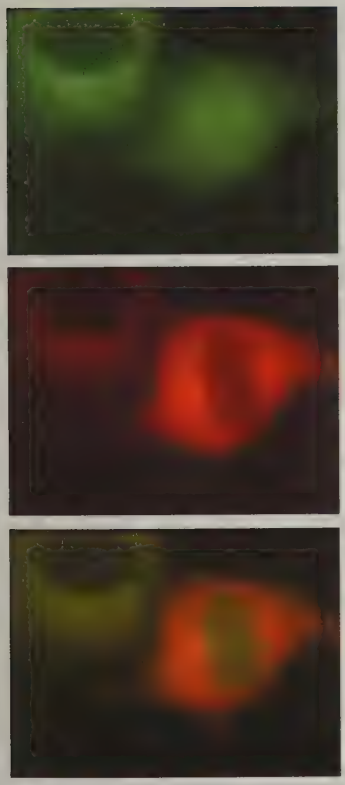
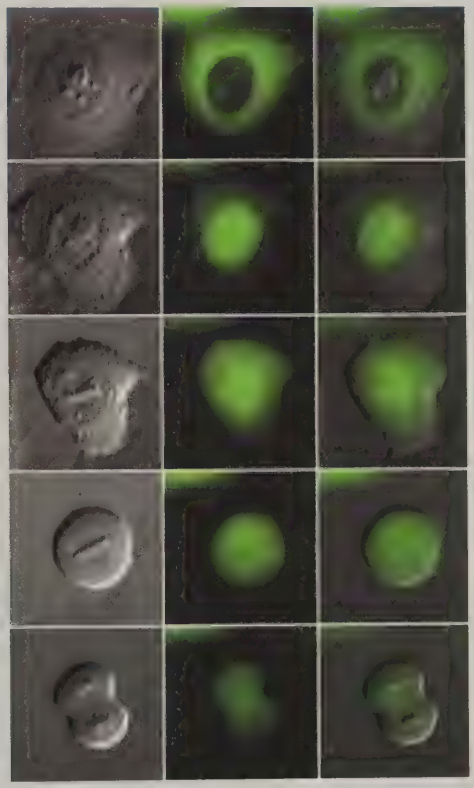
Jackman, M., Firth, M., and Pines, J. (1995). Human cyclins B1 and B2 are localised to strikingly different structures: B1 to microtubules, B2 primarily to the Golgi apparatus. **EMBO J.** *14,* 1646–1654.

Hagting, A., Karlsson, C., Clute, P., Jackman, M., and Pines, J. (1998) MPF localisation is controlled by nuclear export. **EMBO J.** *17,* 4127–4138.

For further publications see page 53.



Cyclin B1–GFP and a mutant form of cyclin B1 linked to yellow fluorescent protein were expressed in *HeLa* cells and visualised with custom filter sets and a cooled slow-scan CCD camera. The mutant cyclin B1 that cannot be phosphorylated in the CRS region enters the nucleus after the wild-type protein.



Cyclin B1–degradation visualised in real time. Cyclin B1–GFP purified from baculovirus-infected cells was injected into a HeLa cell and then imaged with a cooled slow-scan CCD camera. Left panels DIC images, middle panels fluorescence, right panels merged images.

The centrosome is the main microtubule-organising centre in animal cells. Despite its central role in organising many cellular events, very little is known about how centrosomes function. We have taken a reductionist approach to this problem, isolating a number of proteins that can bind to microtubules *in vitro* and are associated with centrosomes *in vivo*. We hope that by studying these proteins we can gain a better understanding of how the centrosome functions.

One of these proteins is a novel protein called MA8. This protein is associated with the centrosome in interphase, and with the centrosome and spindle in mitosis. Injection of anti-MA8 antibodies into early embryos dramatically inhibits mitotic spindle formation. We have now identified a family of human proteins that are related to MA8 and shown that at least one of them has a similar localisation pattern in human cells. We are currently investigating the functions of these human proteins.

Many cell-cycle regulators are associated with centrosomes and we have started to analyse the potential role of the centrosome in regulating cell cycle events. We have made a cyclin B–green fluorescent protein (GFP) construct and shown that the degradation of cyclin B (an event that is crucial for the exit from mitosis) is exquisitely spatially regulated within cells. Cyclin B–GFP accumulates at centrosomes in interphase, in the nucleus in prophase, on the mitotic spindle in prometaphase, and on the microtubules that overlap in the middle of the spindle in metaphase. In cellularised embryos, the protein is degraded in two phases: toward the end of metaphase, degradation of the spindle-associated protein initiates at the spindle poles and spreads to the spindle equator; once complete, the chromosomes enter anaphase, and the remaining cytoplasmic cyclin B is degraded. In mutant embryos, where centrosomes become detached from spindles in early anaphase, cyclin B is degraded on the centrosomes but not on the spindles, and the spindles arrest in anaphase. These observations suggest that, in *Drosophila* embryos, cyclin B degradation requires a connection between the centrosome and spindle.

Huang, J-Y., and Raff, J.W. (1998). The disappearance of Cyclin B at the end of mitosis is spatially regulated in *Drosophila* cells. **EMBO J.** (in press).

Kidd, D., and Raff, J.W. (1997). LK6, a short-lived protein kinase in *Drosophila* that can associate with microtubules and centrosomes. **J. Cell Sci.** *110*, 209–219.

Raff, J.W. (1996). Centrosomes and microtubules: wedded with a ring. **Trends Cell Biol.** *6*, 248–251.

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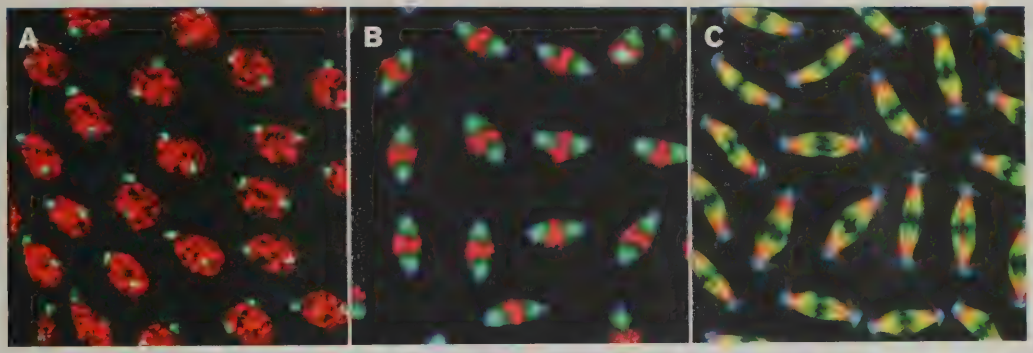
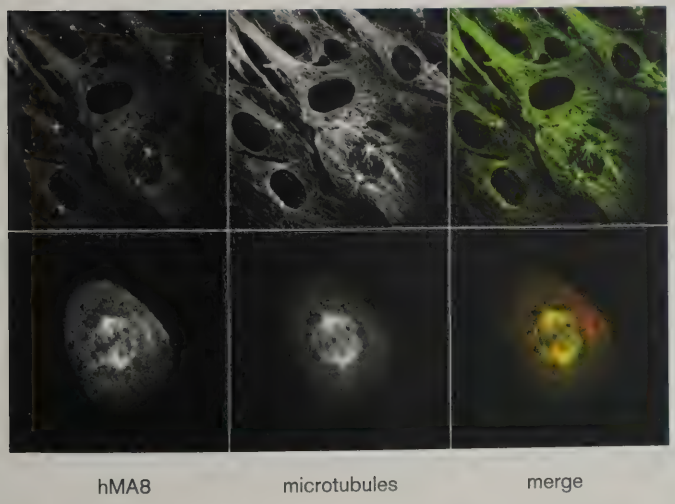


The distribution of the MA8 protein (blue), microtubules (green) and DNA (red) in early embryos at interphase (A), metaphase (B), and anaphase (C). The MA8 protein is located at the centrosome throughout the cell cycle.



The distribution of human MA8-1 (hMA8) in human tissue culture cells. Top: a field of cells in interphase. Bottom: a single cell in mitosis.

The generation of polarity within a cell plays an essential role in many developmental events, such as the determination of body axes, and the asymmetric divisions that generate new cell types. Cell polarity is established by the localisation of specific proteins to each end of the cell, and this is often achieved by localising the mRNAs that encode these proteins. A striking example of this phenomenon is provided by the localisation of bicoid, oskar and gurken mRNAs to three distinct positions within *Drosophila* oocyte. The positions of these mRNAs define the anterior–posterior and dorsal–ventral axes of the embryo. My group is using the *Drosophila* oocyte to investigate the molecular mechanisms that underlie cell polarity and mRNA localisation because it has two important advantages as a model system. Firstly, the oocyte is about 1000-times larger than the average somatic cell, making it very amenable to cell-biological approaches. Secondly, mutations that disrupt mRNA transport or oocyte polarity cause pattern defects in the resulting embryos, and this makes it possible to perform genetic screens to identify the genes required for these processes.

We have shown that the dsRNA-binding protein, Staufen, is required for the localisation of both bicoid and oskar mRNA, and co-localises with each transcript. Furthermore, Staufen targets prospero mRNA to the basal side of dividing neuroblasts. We are currently studying how Staufen recognizes these different mRNAs, and are characterising proteins that interact with Staufen to mediate both actin- and microtubule-dependent mRNA transport. We have also made a fusion between Staufen and green fluorescent protein so that we can watch mRNA localisation in living oocytes.

As many of the factors that are involved in cell polarity and mRNA localisation have not yet been identified, we are carrying out genetic screens to find new genes that act in these processes. So far, we have identified six novel loci, and are characterising their functions in different polarised cell-types.

González-Reyes, A., and St Johnston, D. (1998). The *Drosophila* AP axis is polarised by the cadherin-mediated positioning of the oocyte. **Development** *125*, 3635–3644.

Gonzalez-Reyes, A., and St Johnston, D. (1998). Patterning of the follicle cell epithelium along the anterior–posterior axis during *Drosophila* oogenesis. **Development** *125*, 2837–2846.

Schuldt, A.J., Adams, J.H.J., Davidson, C.M., Micklem, D.R., Haseloff, J., St Johnston, D., and Brand, A.H. (1998). Miranda mediates asymmetric protein and RNA localisation in the developing nervous system. **Genes Dev.** *12*, 1847–1857.

For further publications see page 53.

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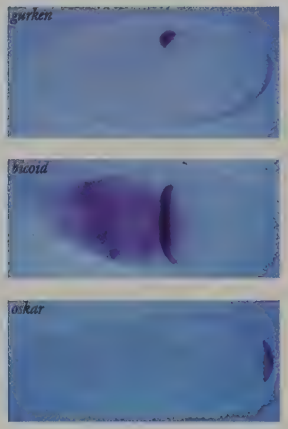
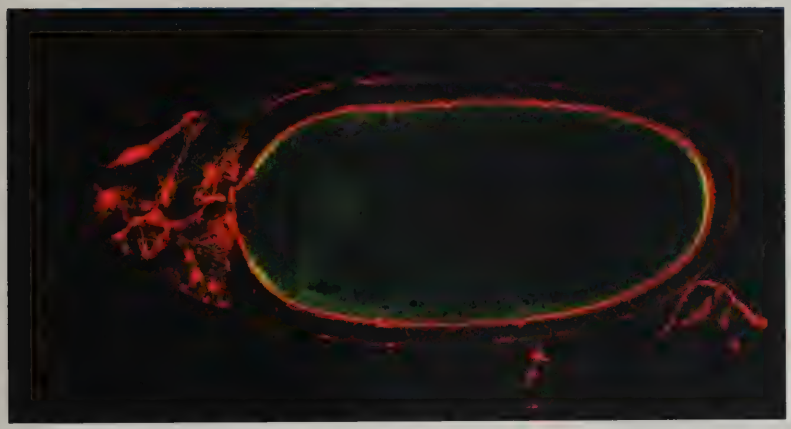
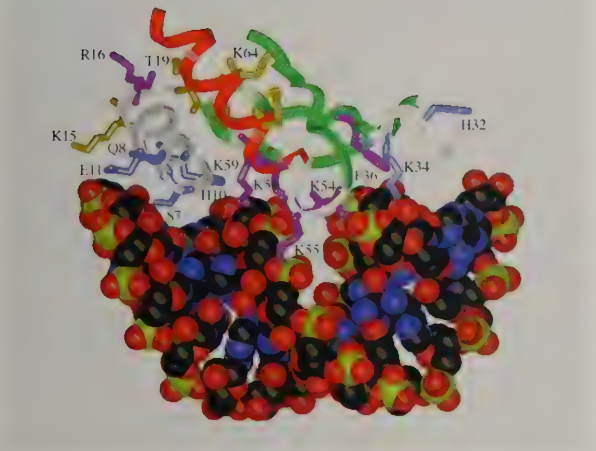


Gurken, bicoid and oskar mRNA localization.



Wild-type egg chamber showing the localisation GFP–Staufen at the anterior of the oocyte with bicoid mRNA and at posterior with oskar mRNA. The egg chamber has been counterstained with rhodamine-phalloidin (red) to reveal the organisation of the actin cytoskeleton.



A model for how a single double-stranded RNA-binding domain from Staufen protein contacts dsRNA. The backbone of the domain is shown as a ribbon with the a-helices in blue, b-sheets in green, and loops in white. The side chains of the amino acids that are required for RNA binding are shown in red and project from one side of the domain. The model shows how these side chains might contact a 12 base pair region of dsRNA (bottom)

We are investigating the properties of the mammalian germ line, in particular the mechanisms involved in genomic imprinting and totipotency. The germ line regulates mammalian development by 'imprinting' epigenetic modifications onto parental genes. The parental genomes therefore function differently in mammalian development because of the preferential expression of one parental allele of each imprinted gene.

When primordial germ cells (PGCs) begin to develop, all the previous epigenetic modifications of the genome are first erased. This is reminiscent of a change from a differentiated to a totipotent genomic state. We are examining the mechanisms of these transformations of developmental state. A somatic cell nucleus can also acquire a totipotent state when exposed to PGC environment in PGC–somatic cell hybrids. At a later stage of development than the PGC, an oocyte can similarly restore totipotency by erasing the epigenetic modifications from somatic nuclei, except perhaps for the germ line-specific parental imprints.

The next stage of germ line-specific epigenetic modifications require *cis* regulatory elements in the imprinted loci. We have identified *cis* control elements by monitoring the activities of modified transgenes in mice. These *cis* elements can also induce gene silencing in *Drosophila,* thus revealing a mechanistic link between gene silencing and genomic imprinting. To understand this link, we plan to study the *trans*-acting factors that interact with the *cis* control elements in both organisms. Conditional deletion of these *cis* elements and the *trans*-acting factors in germ cells, gametes and embryos, will establish their precise functions.

To understand the function of monoallelic imprinted gene dosage, we are focusing on neural development since maternal and paternal genomes contribute unequally to cell allocation during the formation of the central nervous system. Recent studies on *Mest* and *Peg3* demonstrate that these genes with paternal allele-specific expression in the brain affect maternal behaviour.

Tada, M., Tada, T., Lefebvre, L., Barton, S.C., and Surani, M.A. (1997). Embryonic germ cells induce epigenetic reprogramming of a somatic nucleus in hybrid cells. **EMBO J.** *16,* 6510–6520.

Surani, M.A. (1998). Imprinting and the initiation of gene silencing in the germ line. **Cell** *93,* 309–312.

Lefebvre, L., Viville, S., Barton, S.C., Ishino, F., Keverne, E.B., and Surani, M.A. (1998). Abnormal maternal behaviour and growth retardation associated with loss of the imprinted gene *Mest.* **Nature Genet.** *20,* 163–169.

For further publications see page 54.

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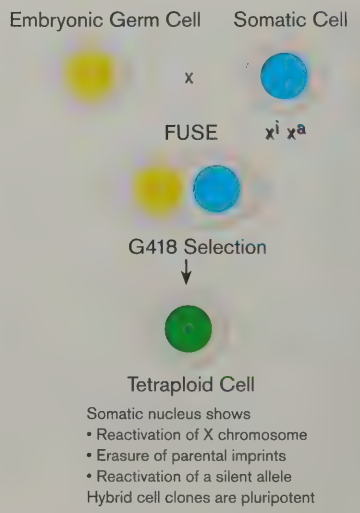
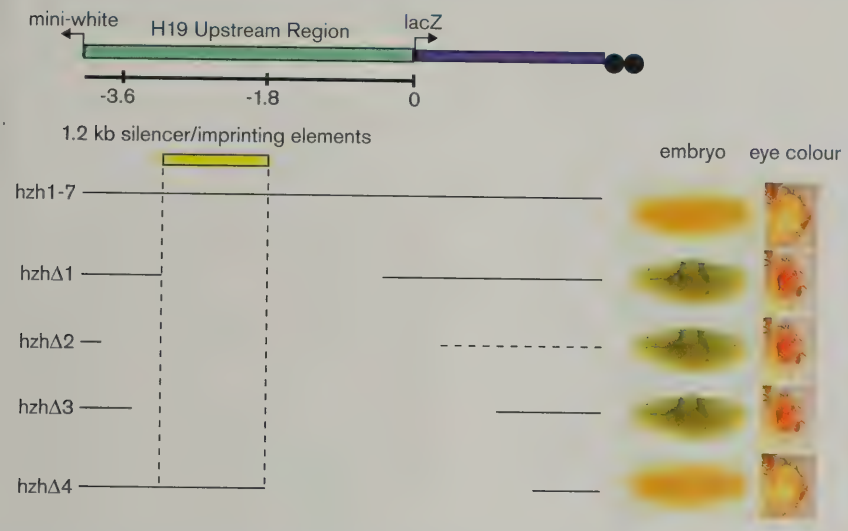
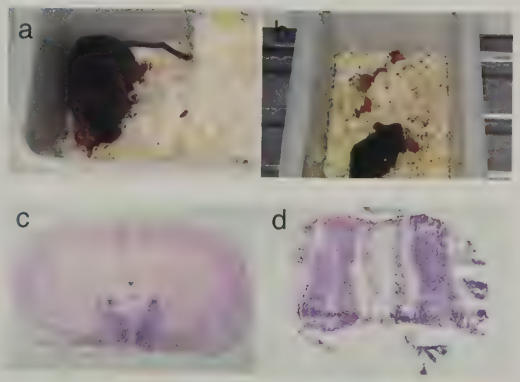




The maternal allele of the H19 imprinted gene is preferentially expressed. An imprinting *cis* element has been detected in the upstream region between -2 and -4kb. The transgene, when introduced into *Drosophila*, led to the identification of a 1.2kb cis element which acts as a bi-directional gene silencer. The overlap between the imprinting/silencer element suggests conservation of certain epigenetic mechanisms in these organisms.

(Left) The somatic cell nucleus undergoes substantial reprogramming through epigenetic modifications in an embryonic germ cell-somatic cell hybrid, accompanied by erasure of the parent of origin-specific methylation of its imprinted loci. This restores expression to a previously silent allele of an imprinted gene. The model makes it possible to investigate mechanisms by which a somatic nucleus acquires a pluripotent state.



(Right) Imprinted genes affect aspects of development and behaviour in mammals. Mutations in the *Peg3* and *Mest* genes affect maternal behaviour. The wild-type animal shows appropriate maternal care (a) whereas the mother with the mutation in these genes fails to respond appropriately to the new born offspring (b). The genes are expressed in the adult brain including the hypothalamus (c) and the olfactory bulbs (d). Both genes are expressed only when inherited from the father, whereas the maternal allele is repressed. These studies have implications for evolutionary theories of genomic imprinting, and for the role of paternally inherited genes affecting behaviour.

When germ cells are isolated from mouse embryos and cultured in the presence of appropriate growth factors, they will proliferate indefinitely as embryonic germ (EG) cell lines. EG cells have been derived from germ cells both before their migration has started, and later, when they have colonized the gonad but before they enter meiosis (in female embryos) or mitotic arrest (in male embryos). We are interested in establishing immortalized cell lines from migrating germ cells, when their properties change dramatically, and also from germ cells after birth, to explore further the establishment of new methylation patterns in imprinted genes.

The transformation from germ cell to EG is poorly understood. There are many similarities but also differences between the two cell types. Primordial germ cells, but not EG cells, will enter meiosis in a tissue aggregate maintained in an organ culture system. EG cells, but not primordial germ cells, will colonize all the cell lineages of the developing embryo if injected back into a blastocyst. There are also differences in gene expression and in antigenic properties. We are studying how the transformation from germ cell to EG cell takes place, in order to throw light on the molecular basis of totipotency, and studying the regulatory mechanisms that determine the cyclical nature of differentiation in the germ cell lineage.

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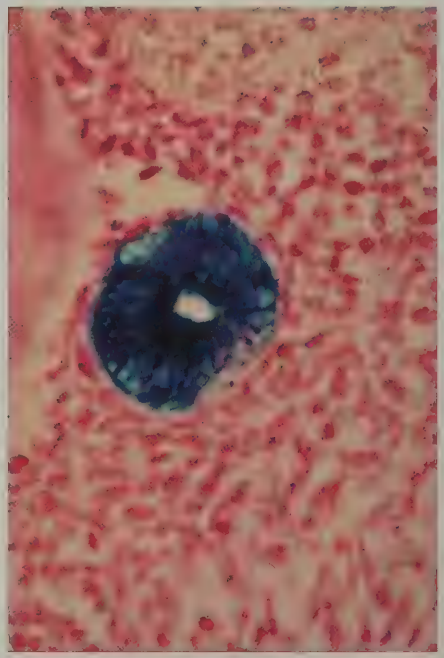

EG cells (blue) from an EG cell line transgenic for β-galactosidase differentiating in a reaggregate of mouse embryonic genital ridge cells, cultured for five days.

McLaren, A. (1998). Gonad development: assembling the mammalian testis. **Curr. Biol.** *8*, R175–R177.

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McLaren, A. (1998) Germ cells and germ cell transplantation. **Int. J. Dev. Biol.** *42*, 855–860.

McLaren, A. (1999) Signalling for germ cells. **Genes Dev.** *13*, in press.

For further publications see page 52.

CATEGORIES OF APPOINTMENT

Principal Group Leader	Professor, Reader or Lecturer level
Younger Group Leader	5 year grant-funded appointment (maximum 10 years)
Career Development Fellow	4 year grant-funded appointment
Independent Senior Research Associate	3 year grant-funded appointment
Research Associate / Fellow	Postdoctoral, within individual groups, appointed by group leader
Graduate Student	3 year studentship within individual groups, mainly grant-funded
Research Assistant	Postgraduate, within individual groups, mainly grant-funded
Research Technician	Within individual groups, mainly grant-funded
Laboratory Assistant	Within individual groups or part of core support; grant funded

POSTGRADUATE OPPORTUNITIES

As part of the University of Cambridge, the Institute welcomes enquiries from prospective graduate students. We have a thriving population of graduates who contribute greatly, not only to the stimulating research environment, but also to the life of the Institute as a whole. Additionally, graduates become members of the biological or medical sciences department to which their group is affiliated. Graduate studentships are supported mainly by the Wellcome Trust or Cancer Research Campaign but additional sponsorship may be solicited from a variety of sources, including government research councils.

Applicants should write, in the first instance, to the leader of the group they wish to join.

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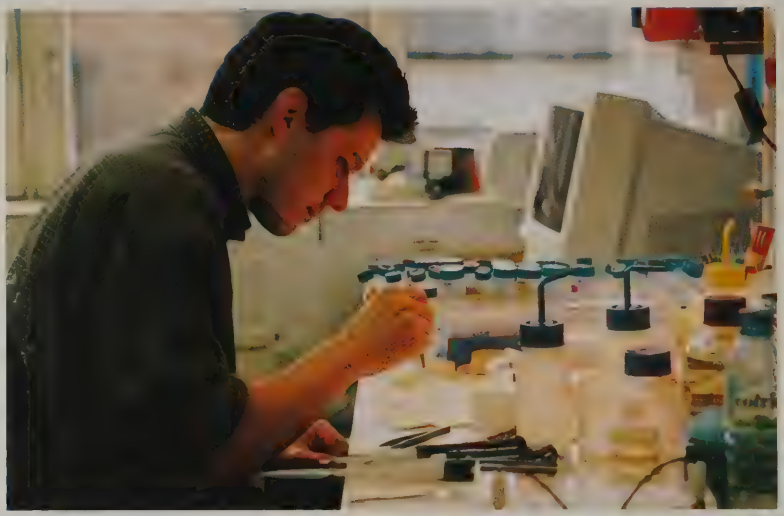

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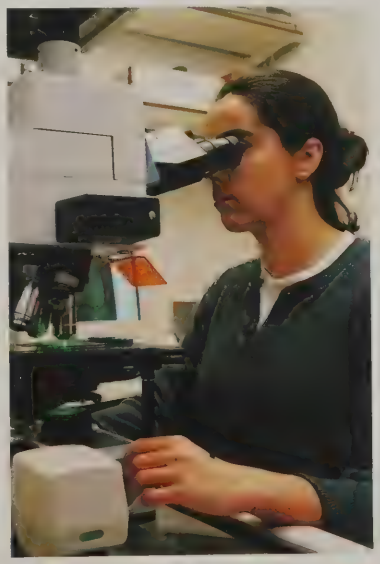

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AHRINGER GROUP

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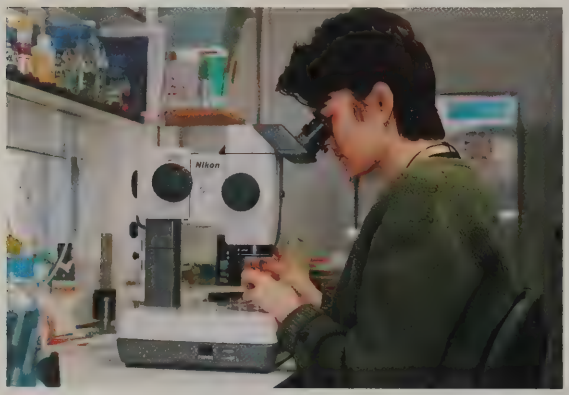

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OTHER ACTIVITIES

JULIE AHRINGER is a Board Member of the British Society of Developmental Biology.

ANDREA BRAND is a member of the Scientific Advisory Board for the Promega Corporation.

CHARLES FFRENCH-CONSTANT is a Consultant in Medical Genetics at Addenbrooke's Hospital, Cambridge.

JOHN GURDON is a Governor of the Wellcome Trust.

STEVE JACKSON is a member of the Biochemical Society Nucleic Acids and Molecular Biology Group Committee, the Biochemical Society Council, and the European Molecular Biology Organization.

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RON LASKEY is President of the British Society of Cell Biology, a member of the Cancer Research Campaign Scientific Committee, and a Trustee of Strangeways Research Laboratories.

ANNE McLAREN is a member of the Human Fertilization and Embryology Authority, the Nuffield Bioethics Council, and the European Group on Ethics – an advisory group to the European Commission – also a Trustee of the Natural History Museum.

DANIEL ST JOHNSTON is a Board Member of the British Society of Developmental Biology, an Executive Director of the Company of Biologists and is a member of the European Molecular Biology Organization.

AZIM SURANI is a member of the Royal Society International Exchange Panel.

HONOURS AND AWARDS

ANDREA BRAND Research Fellow, King's College

CHARLES FFRENCH-CONSTANT 1998 MacKeith Lecture to British Paediatric Neurology Association

JOHN GURDON Doctor of Science, Honoris causa, University of Hull. Special lectures: Verna & Marrs McLean Lecture, Baylor College of Medicine, Houston, USA; Friday Lecture Series, Rockefeller Institute, USA.

RON LASKEY received the CIBA medal of the Biochemical Society and was awarded the Feldberg Prize and the 1998 Louis-Jeantet Prize for Medicine (Switzerland).

AZIM SURANI The Raffles Lectures, Institute of Molecular & Cell Biology, Singapore.

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